JCI The Journal of Clinical Investigation

THE PULMONARY BLOOD VOLUME IN MAN

Donald S. Dock, William L. Kraus, Lockhart B. McGuire, John W. Hyland, Florence W. Haynes, Lewis Dexter

J Clin Invest. 1961;40(2):317-328. https://doi.org/10.1172/JCI104259.

Research Article

THE PULMONARY BLOOD VOLUME IN MAN *

By DONALD S. DOCK,† WILLIAM L. KRAUS,‡ LOCKHART B. McGUIRE,§ JOHN W. HYLAND,§ FLORENCE W. HAYNES AND LEWIS DEXTER

(From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.)

(Submitted for publication August 8, 1960; accepted October 7, 1960)

The measurement of blood volume in the pulmonary vascular bed during life became theoretically feasible with the introduction of indicator dilution methods by Stewart (1) and Hamilton, Moore, Kinsman and Spurling (2). The principles and formulas set forth by these investigators have since undergone extensive scrutiny by theoretical analysis, in circulation models, and *in vivo*. As a result of these studies, there exists now general agreement that the introduction of an indicator substance into the central circulation, either directly or by peripheral venous injection, and downstream recording of its concentration change with time during the first transit permits the determination of three important circulatory parameters: *1*) the cardiac output, *2*) the mean transit time from injection to sampling site, and *3*) by multiplication of cardiac output and mean transit time, the circulating volume of blood between injection and sampling sites, including all temporally equidistant points in the vascular bed.

Practically speaking, then, the measurement of pulmonary blood volume *in vivo* requires determination of the mean transit time of an indicator from the pulmonary artery to the left atrium together with cardiac output.

The development of right and left heart catheterization has made the pulmonary artery and left atrium accessible as injection and sampling sites in man. Injection of an indicator through a cardiac catheter into the pulmonary artery is easy. The recording of dilution curves by sampling from the left atrium is feasible but cumbersome. Furthermore, it is uncertain whether an indicator injected into the pulmonary artery and sampled from the left atrium will undergo complete mixing, since it does not traverse a ventricular chamber in which turbulent flow exists.

In the present study, an attempt was made to measure pulmonary blood volume in man by the Stewart-Hamilton method and yet avoid left atrial sampling and the uncertainty of adequate mixing in the pulmonary circuit. The procedure employed was the simultaneous injection of two different indicators into the pulmonary artery and left atrium, with sampling from the brachial artery. This yields duplicate determinations of cardiac output as well as the mean transit time of indicator A from the pulmonary artery to the brachial artery and of indicator B from the left atrium to the brachial artery. By subtraction, the mean transit time from pulmonary artery to left atrium is obtained, and pulmonary blood volume can be calculated. Both indicators traverse the left ventricle where they are exposed to a common degree of turbulent mixing. The use of a common collecting system ensures that any distortion of the time-concentration curves due to its particular properties would affect both indicators equally and thus, in effect, cancel out. The principle of the determination is represented schematically in Figure 1.

Since the method requires simultaneous catheterization of the right and left heart, no observations in normal subjects were carried out. The determinations were made in the course of diagnostic studies on 45 adult patients who had or were suspected of having mitral or aortic valvular disease of sufficient complexity to warrant combined right and left heart catheterization for evaluation of their cardiac status.

* This work was supported in part by grants from the Life Insurance Medical Research Fund, the American Heart Association, and the National Heart Institute, (Grant no. H-450), Bethesda, Md.

† Work done during the tenure of a Research Fellowship from the American Heart Association. Present address: Dept. of Pediatrics, Yale University School of Medicine, New Haven, Conn.

‡ Work done during the tenure of a Postdoctoral Fellowship from the Life Insurance Medical Research Fund.

§ Work done during the tenure of a Postdoctoral Research Fellowship from the National Heart Institute, Bethesda, Md.

SCHEMA OF CIRCULATION TO ILLUSTRATE DETERMINATION OF PULMONARY BLOOD VOLUME

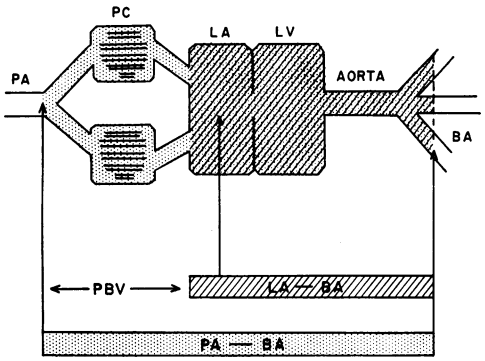

FIG. 1. TWO INDICATORS ARE INJECTED SIMULTANEOUSLY INTO PULMONARY ARTERY (PA) AND LEFT ATRIUM (LA) AND SAMPLED FROM BRACHIAL ARTERY (BA). The difference between the two mean transit times, multiplied by the cardiac output, equals the pulmonary blood volume (PBV). See text for details.

MATERIAL AND METHODS

Pulmonary blood volume was determined in 45 patients, ranging in age from 22 to 60 years, average age, 41 years. There were 19 males and 26 females, none of whom had congenital heart disease or circulatory shunts. In most instances, combinations of valvular lesions were present. The classification employed throughout this report groups the patients according to the defect which was considered the hemodynamically preponderant one on the basis of clinical picture, catheterization findings and, wherever applicable, subsequent surgical observations. By these criteria, 15 patients had predominant mitral stenosis, 13 predominant mitral regurgitation, 7 predominant aortic stenosis, 3 predominant aortic regurgitation. There were 3 patients with equally significant mitral and aortic valve disease; of these 1 had stenosis of both valves, 1 had both mitral and aortic regurgitation, and 1 had aortic stenosis and mitral regurgitation. Four patients had no demonstrable hemodynamic derangement. The final diagnoses in these were coronary artery disease in 1, restrictive pleuritis in 1, and no demonstrable cardiac or pulmonary abnormality in 2. This group of 4 patients will be referred to subsequently under the heading "normal circulatory dynamics."

All patients were studied in the fasting state, premedicated with 100 mg secobarbital orally and 50 to 75 mg meperidine intramuscularly. In some instances, an additional 8 mg morphine sulfate was given intramuscularly just before the left heart catheterization. A venous catheter (size 6 or 7F, 125 cm in length) was introduced under local procaine anesthesia via the right antecubital vein, and its tip placed in the right or left main pulmonary artery, just beyond the bifurcation of the pulmonary trunk. The left brachial artery was cannulated with a no. 16 gage Cournand needle. The patient was then turned to the prone position and left heart catheterization performed by the percutaneous paravertebral route as previously described (3), introducing a no. 16 gage thin-walled needle into the left atrium. A 40 cm length of PE60 polyethylene tubing was passed through the lumen of the needle, advanced across the mitral valve for pressure measurements in the left ventricle, and then withdrawn until its tip rested in the left atrium. Pressures were recorded through Statham P23D strain gage manometers on a Sanborn Polyviso direct-writing oscillograph. The zero point for all pressure measurements was taken to be 10 cm anterior to the skin of the back at the level of the seventh thoracic vertebra. Immediately after the simultaneous recording of pressures in the pulmonary artery, left atrium and brachial artery, the indicator dilution studies were carried out. Upon a prearranged signal, simultaneous rapid injections were made of 3 ml Evans blue dye into the pulmonary artery and 3 ml I^{131}-labeled human serum albumin (6 to 8 μc per ml) into the left atrium, while blood was allowed to flow from the arterial needle through a 28 cm length of PE280 polyethylene tubing (volume 1.0 ml) into a rotating wheel-type fraction collector containing test tubes with a few crystals of dried heparin. Each tube collected blood for exactly 2 seconds. The time and duration of the left atrial injection and the passage of the sampling tubes were inscribed on the Polyviso record via electric relay switches. The recorded duration of the injection was usually 1 second; the midpoint of the injection period was considered zero time for all transit time measurements. Gibson syringes were used for all indicator injections; the amount delivered from syringe and catheter was calibrated by weight. After completion of the procedure, all sample tubes were centrifuged, and 0.5 or 1.0 ml aliquots of undiluted plasma analyzed for radioactivity in a well-type scintillation counter for sufficient time to ensure less than 1 per cent error. In some instances during earlier experiments, the radioactivity determinations were performed on similar aliquots of whole blood pipetted from the sample tubes after gentle agitation prior to centrifugation. Dye concentration in the undiluted plasma was then determined on the same specimens in a Beckman DU spectrophotometer using Pyrocell microcuvets, reading extinction at 620 mμ against a blank of the patient's own plasma. Standards of the radioactive injectate were prepared in quadruplicate by 1:1,000 dilution in normal saline. Dye standards were prepared by quantitative dilution of the injectate in each patient's own plasma. Aliquots of the injectate standards were analyzed for radioactivity and dye concentration in the same manner as the samples. Hematocrits were determined in quadruplicate on samples from the fraction collector immediately preceding and following the appearance of the indicator curves, by spinning with a centrifuge radius arm of 19 cm for 30 minutes at 3,000 rpm in Wintrobe tubes, and corrected for trapped plasma as advocated by Gregersen (4). Time-concentration curves were plotted on semilogarithmic graph paper for

each indicator and extrapolated through three logarithmic cycles from the onset of the straight-line downslope. Cardiac output and mean transit time were calculated from each curve by the usual Stewart-Hamilton formulas (1, 2) as follows:

$$\text{C.O.} = \frac{(60)(\text{Vol. I})(\text{Conc. I})}{(\Sigma\ \text{Conc.})(1 - \text{Hct})}$$

$$\text{MTT} = \frac{\Sigma(\text{Conc.} \times \text{Time})}{\Sigma\ \text{Conc.}}$$

where

C.O. = cardiac output (L/min)
MTT = mean transit time (sec)
Vol. I = volume of indicator injected (ml)
Conc. I = concentration of indicator injected
Σ Conc. = sum of the concentrations read at 1-second intervals from the indicator dilution curve, extrapolated through 3 logarithmic cycles
Time = time at which each concentration occurred, in seconds, from midpoint of injection period
Hct = hematocrit, corrected for trapped plasma = observed Hct × 0.96.

Delay in the collecting system was calculated as follows:

$$\text{delay} = \frac{\text{collecting system volume (1.0 ml)}}{\text{rate of flow (ml/sec)}}.$$

The calculated delay was subtracted from all mean transit time measurements.

The average of the two cardiac output measurements as calculated from the I^{131} curve and from the Evans blue dye curve was used for all volume calculations except for a few instances in which a part of either the radioactive iodine or the dye was lost from the syringe during the process of injection. These situations do not involve an error in the mean transit time calculation for that indicator. The following volume calculations were carried out:

PA → BA volume = C.O. (ml/sec) × MTT PA → BA (sec)

LA → BA volume = C.O. (ml/sec) × MTT LA → BA (sec)

Pulmonary blood volume = C.O. (ml/sec) × (MTT PA → BA − MTT LA → BA)(sec).

RESULTS

The results of the study are listed in Table I, together with the pertinent hemodynamic parameters.

Cardiac output

There was substantial agreement between the simultaneous cardiac output determinations, as shown in Figure 2. The average ratio of the flows as calculated from left atrial and pulmonary arterial injections was 0.98, with a standard deviation, computed from the distribution of ratios, of 0.15.

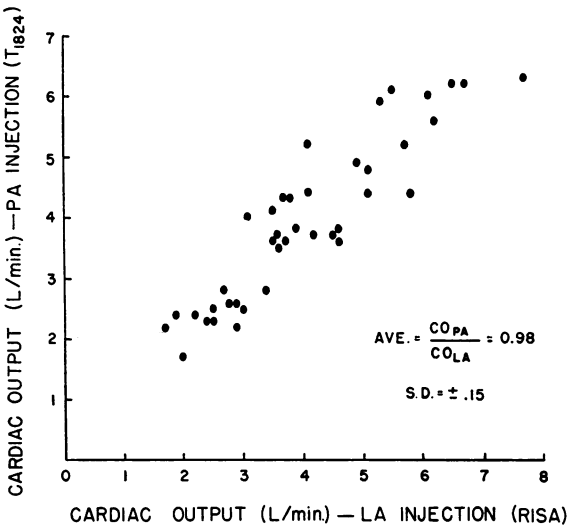

FIG. 2. SIMULTANEOUS CARDIAC OUTPUTS OBTAINED BY INDICATOR DILUTION TECHNIQUE, USING T-1824 INJECTED INTO PULMONARY ARTERY AND RADIO-IODINATED SERUM ALBUMIN (RISA) INJECTED INTO LEFT ATRIUM.

No systematic differences between the two determinations were found, although there were occasional divergences for which no obvious explanation could be offered.

Mean transit time

Pulmonary mean transit time. The mean transit time from pulmonary artery to left atrium varied widely, between the extremes of 3.2 and 28.0 seconds [1.9 and 15.2 seconds per m^2 body surface area (BSA)], with an average of 9.1 seconds (5.6 per m^2) for the entire group. It tended to be more prolonged in the patients with mitral valve disease—average 10.7 seconds (6.4 per m^2) in the mitral stenosis group; 9.2 seconds (5.9 per m^2) in the mitral regurgitant group; and 9.6 seconds (6.2 per m^2) in the three patients with combined mitral and aortic disease. The mean for the patients with aortic valve disease was 7.8 seconds (4.8 per m^2) and for the group with normal circulatory dynamics, 5.3 seconds (3.5 per m^2). Much overlap of values was evident among the different groups.

Mean transit time from left atrium to brachial artery. With the exception of five outstandingly prolonged values in patients with severe mitral regurgitation (18.4 to 34.5, 13.0 to 24.5 seconds per m^2), the transit times between left atrium and brachial artery ranged from 3.1 to 14.8 seconds

TABLE I

Hemodynamic data

Name	Age	Sex	BSA	Cardiac output PA injection	Cardiac output LA injection	Average cardiac index	MTT PA-BA	MTT LA-BA	MTT PA-LA	Blood volume PA-BA	Blood volume LA-BA	Pulmonary blood volume, PA-LA	Mean pressure PA	Mean pressure LA	Pulmonary vascular resistance	Left atrial size (X-ray*)
			m²	*L/min*		*L/min/m²*	*sec*	*sec*	*sec*	*ml/m²*	*ml/m²*	*ml/m²*	*mm Hg*		*dynes-sec-cm⁻⁵*	
Normal circulatory dynamics																
E.K.	42	F	1.68	5.2	4.1	2.7	9.1	4.3	4.8	415	196	219	14	7	122	N
J.P.	54	M	1.76	6.3	7.7	4.0	9.8	6.2	3.6	648	411	239	16	6	114	N
F.F.	44	M	1.99	6.2	6.5	3.2	12.9	8.1	4.8	691	434	257	16	8	100	1+
W.H.	60	M	1.98		4.1	2.1	15.0	7.2	7.8	518	248	269	20	6	273	N
Predominant mitral stenosis																
C.K.	26	F	1.56	4.4	4.1	2.7	8.8	4.5	4.3	395	202	193	18	7	209	1+
M.B.	38	F	1.75	3.6	4.6	2.3	11.5	6.4	5.1	449	250	199	19	9	195	1+
G.H.	45	F	1.65	3.7	3.6	2.2	14.6	7.6	7.0	545	284	262	36	30	130	2+
P.M.	47	F	1.42		3.7	2.6	13.0	6.8	6.2	565	295	269	30	19	238	2+
M.Mc	36	F	1.53	2.5	3.0	1.9	18.6	9.6	9.0	567	293	275	32	20	343	2+
T.F.	41	M	1.89	1.7	2.0	1.0	29.2	12.1	17.1	489	203	287	59	27	1,346	2+
R.M.	44	F	1.57	5.6	6.2	3.8	7.8	3.1	4.7	489	194	294	28	18	135	1+
E.F.	47	F	1.57	2.3	2.5	1.5	21.6	9.1	12.5	550	232	318	94	40	1,798	2+
J.H.	30	F	1.37	2.8	2.7	2.0	18.9	9.1	9.8	621	299	322	85	33	1,539	2+
F.F.	45	M	1.66	4.3	3.8	2.5	16.4	8.5	7.9	675	350	325	68	30	741	2+
C.D.	42	F	1.56	3.6	3.7	2.4	13.1	4.7	8.4	518	186	332	61	36	540	2+
W.P.	43	F	1.47	3.7	4.5	2.8	14.2	6.9	7.3	660	321	339	25	21	78	2+
B.R.	30	F	1.82	4.0	3.1	2.0	25.2	10.8	14.4	831	356	475	94	40	1,199	2+
O.G.	46	M	1.83		3.0	1.6	32.9	14.8	18.1	899	404	495	28	22	160	2+
J.Z.	48	M	1.84	2.5	2.5	1.4	40.9	12.9	28.0	926	292	634	36	23	416	2+
Predominant mitral regurgitation																
M.G.	45	F	1.67	4.1		2.5	9.5	5.3	4.2	389	217	172	66	21	877	2+
M.C.	44	F	1.41	2.2	1.7	1.4	42.8	34.5	8.3	1,012	816	196	47	32	599	4+
I.R.	27	F	1.32	4.1	3.5	2.9	11.0	6.2	4.8	527	298	230	13	9	84	1+
A.E.	38	M	1.92	2.3	2.4	1.3	32.0	19.4	12.6	667	404	263	51	31	666	3+
J.R.	36	F	1.48	3.8	3.9	2.6	12.3	5.8	6.5	541	255	286	14	5	184	2+
M.C.	38	F	1.37	2.6	2.8	2.0	27.5	18.6	8.9	904	611	293	49	27	651	3+
E.H.	35	F	1.56	6.0	6.1	3.9	9.7	4.3	5.4	622	276	346	16	6	133	2+
McQ.	49	F	1.26	2.6	2.9	2.1	39.2	29.1	10.1	1,400	1,039	361	39	19	592	3+
G.P.	27	F	1.42	2.2	2.9	1.8	30.7	18.4	12.3	901	540	361	24	15	288	3+
H.T.	60	M	1.90		3.2	1.7	28.3	13.8	14.5	794	387	407	56	21	874	2+
A.C.	45	F	1.52	3.7	4.2	2.6	19.6	10.0	9.6	860	432	421	29	25	80	3+
R.B.	44	M	2.07	4.4	5.1	2.3	21.1	7.8	13.3	799	295	503	39	22	289	2+
M.S.	45	F	1.55	4.4	5.8	3.3	18.0	8.5	9.5	987	466	521	24	19	78	3+
Predominant aortic stenosis																
J.D.	56	M	1.80	3.5	3.6	2.0	17.8	12.1	5.7	577	392	185	19	12	160	N
A.P.	51	M	1.78	6.1	5.5	3.3	11.8	7.7	4.1	641	418	223	16	13	41	2+
S.S.	41	M	1.68	4.9	4.9	2.9	12.5	7.9	4.6	608	384	224	21	13	130	2+
K.W.	31	M	1.82	4.8	5.1	2.7	12.9	5.6	7.3	579	251	328	17	7	163	N
V.D.	45	F	1.50	3.8	4.6	2.8	12.3	5.0	7.3	574	233	341	9	1	152	N
J.W.	34	M	1.58	3.6	3.4	2.3	16.4	5.9	10.5	623	224	399	23	8	333	N
L.P.	22	M	1.62	4.3	3.7	2.5	20.6	10.3	10.3	848	424	423	38	22	320	2+
Predominant aortic regurgitation																
N.W.	35	F	1.66	5.2	5.7	3.3	7.8	4.6	3.2	431	254	177	11	3	116	N
W.P.	41	M	1.65	6.2	6.7	3.9	20.5	14.3	6.2	1,325	924	401	50	22	350	2+
J.L.	39	M	1.86	2.8	3.4	1.7	33.7	14.7	19.0	936	409	527	52	15	954	2+
Combined mitral and aortic lesions																
T.D.	45	F	1.47	2.4	2.2	1.6	18.5	11.2	7.3	482	292	190	21	15	209	2+
J.B.	36	M	1.90	5.9	5.3	3.0	15.3	8.3	7.0	752	408	344	24	13	157	2+
L.F.	39	F	1.48	2.4	1.9	1.5	24.1	9.6	14.5	597	238	359	63	23	1,453	2+

* Arbitrary assessment of size on basis of normal (N) to 4+.

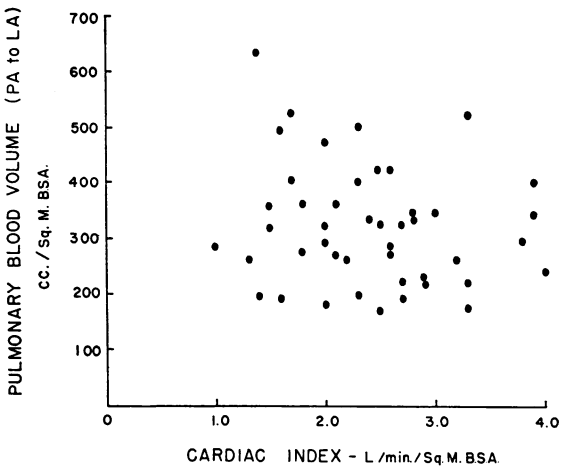

FIG. 3. RELATIONSHIP BETWEEN CARDIAC OUTPUT AND PULMONARY BLOOD VOLUME. There is no evident correlation between pulmonary blood flow and pulmonary blood volume.

(2.0 to 8.1 per m^2), with no notable differences between the different groups. In the four patients with normal circulatory dynamics, the range was 4.3 to 8.1 seconds (2.6 to 4.1 per m^2).

Pulmonary blood volume

The pulmonary blood volume was found to range from 172 to 634 ml per m^2 BSA, with a mean of 322 ml per m^2 for the entire group. The patients with mitral valve disease tended to show slightly higher values than the remainder, the mean for the mitral stenosis group being 335, for mitral regurgitation 335, for combined mitral and aortic disease 298, and for all patients with mitral disease 331 ml per m^2 as against 323 ml for those with aortic disease alone and 246 for the subjects with normal circulatory dynamics. There was much overlap among the groups, and the sample of patients without mitral disease was too small to assign statistical significance to the difference between the means.

Volumes between left atrium and brachial artery

Four patients with mitral regurgitation and one with aortic regurgitation were found to have marked increases of blood volume, relative to the other cases, in the compartment which includes the chambers of the left heart and portions of the proximal arterial tree. The calculated volumes in these five patients ranged from 540 to 1,039 ml per m^2 BSA, and all showed marked enlargement of the left atrium and ventricle by X-ray. All remaining patients fell in a range of volumes from 186 to 466 ml per m^2, without significant differences between the different groups. In general, the pulmonary blood volume and the volume between left atrium and brachial artery tended to be of approximately equal size.

Correlations

Possible correlations between the calculated pulmonary blood volume and various simultaneously measured hemodynamic parameters were examined. Since pulmonary blood volume is the product of cardiac output and mean transit time, a correlation with one or the other of these two factors is inherent in the calculation. No correlation with cardiac output was found (Figure 3), but higher pulmonary blood volumes were associated with longer pulmonary mean transit times (Figure 4) ($R = +0.769$). There was also an inverse relationship between cardiac index and pulmonary mean transit times (Figure 5). The correlation coefficient, utilizing the logarithmic transformation of the pulmonary mean transit time, was -0.742. No correlation was found between pulmonary blood volume and pulmonary vascular resistance or pressure difference across

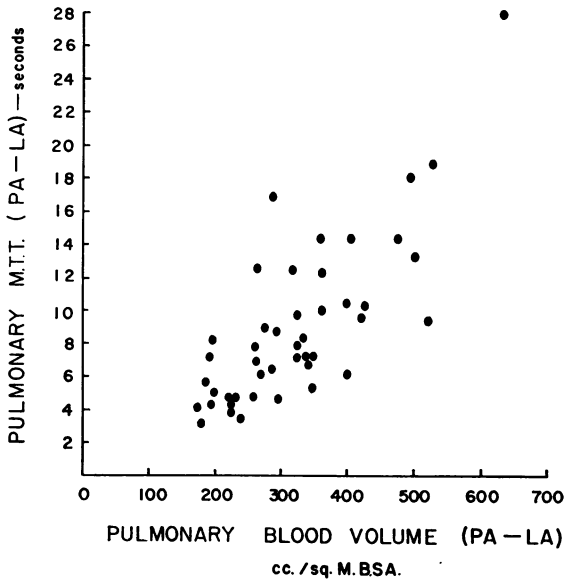

FIG. 4. RELATIONSHIP BETWEEN PULMONARY BLOOD VOLUME AND PULMONARY MEAN TRANSIT TIME. A significant direct correlation is seen between pulmonary blood volume and mean transit time, i.e., the pulmonary blood volume varies inversely with the velocity of blood flow.

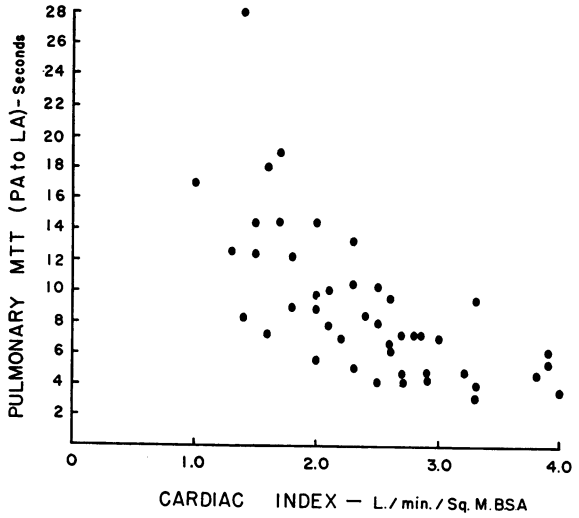

FIG. 5. RELATIONSHIP BETWEEN CARDIAC INDEX AND PULMONARY MEAN TRANSIT TIME. There is a direct correlation between pulmonary blood flow and velocity.

the pulmonary circulation (pulmonary arterial mean minus left atrial mean pressures). Figures 6 and 7 show plots of pulmonary blood volume against pulmonary arterial mean pressure and left

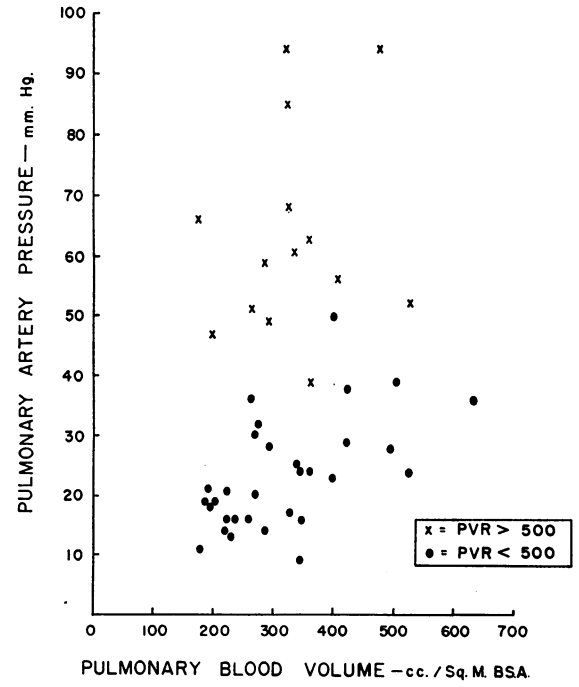

FIG. 6. RELATIONSHIP BETWEEN PULMONARY ARTERY PRESSURE AND PULMONARY BLOOD VOLUME. There is a correlation between the volume of blood in the lungs and the pulmonary arterial pressure, which is most evident in those cases without marked elevation of pulmonary vascular resistance. See text for statistical significance.

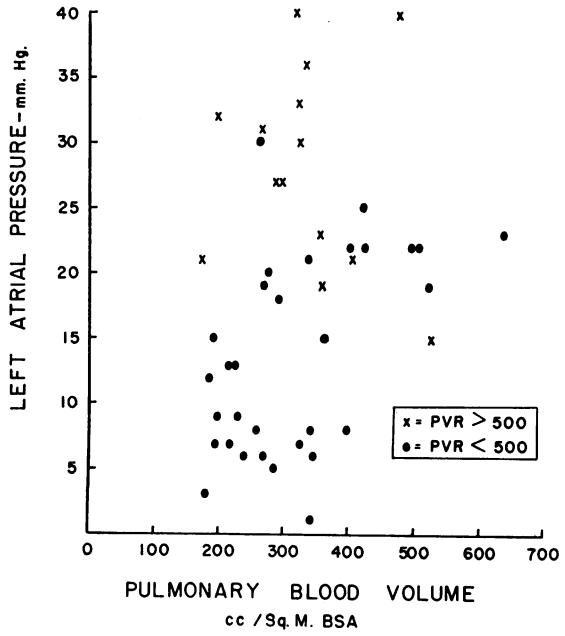

FIG. 7. RELATIONSHIP BETWEEN LEFT ATRIAL PRESSURE AND PULMONARY BLOOD VOLUME. An apparent correlation exists between left atrial pressure and pulmonary blood volume, particularly in the low resistance group.

atrial mean pressure. If all cases are included, no significant correlation exists, the R values being 0.258 and 0.283, respectively. On the other hand, if patients with pulmonary vascular resistances above and below 500 dynes-sec-cm^{-5} are considered separately, as in Figures 6 and 7, a tendency for increased pressures to be associated with increased volumes becomes apparent as long as the vascular resistance remains below 500 dynes-sec-cm^{-5}. Excluding the cases with resistances above this level, the correlation coefficients were 0.582 and 0.524, respectively, both being highly significant ($p < 0.001$). Those patients with severely elevated pulmonary vascular resistances tended to have lower volumes than might have been expected from the pressure-volume relationship in the low resistance group.

There was no evident correlation between the volume of the pulmonary vascular compartment and the age, sex or BSA of these adult patients.

DISCUSSION

Consideration of possible errors of the method

The validity of measuring pulmonary blood volume by the method employed rests on certain assumptions.

1. Proportionality of indicator to flow and velocity of flow through the two lungs. Either the indicator injected into the pulmonary artery must be equally distributed to the two lungs, or if it is not equally distributed, the velocity of flow through the two lungs must be identical. There is no reason to believe that indicator injected into the main pulmonary artery or into one branch becomes equally distributed in each main branch. In fact, the probability is that it does not. If the bolus of indicator is diverted predominantly to one lung, the pulmonary mean transit time affords calculation of the blood volume of that lung plus the volume of temporally equidistant vessels of the opposite lung. For the true blood volume of the latter to be included, it is necessary to assume equal velocity of blood flow through both lungs. This assumption has not been tested.

2. Bronchial circulation. The bronchial circulation anastomoses with the pulmonary circulation at the arterial, capillary, and venous levels (5). The flow is said to amount to between 2 and 5 per cent of the cardiac output in normal man. The temporally equidistant portions of these bronchial collaterals entering the lung are included in both the pulmonary arterial and left atrial injection volumes and therefore cancel out when these two are subtracted from one another to arrive at the calculation of pulmonary blood volume. If, however, blood passes from pulmonary artery to the bronchial system as a result of a higher pressure in the pulmonary than in the corresponding systemic circulation, the calculated pulmonary blood volume would be artifactually large, due to an inclusion of this right to left volume which would not be included in the left atrial to brachial arterial volume. It seems unlikely that such a pulmonary to bronchial shunt would be of important magnitude.

3. Mixing of indicator in left atrium. In the event of incomplete mixing of indicator injected into the left atrium, the calculated pulmonary blood volume would include that portion of the chamber volume in which the left atrial injectate did not mix and would thus be falsely high. Evidence indicates that there may indeed be incomplete mixing of indicator within the left atrium, and the extent of incomplete mixing would presumably be dependent upon the indicator's being uniformly distributed in all parts of the atrium, and this would be affected in part by the time of indicator injection relative to the cardiac cycle. The degree to which this mixing factor influences the results of this study cannot be determined at present. Although mixing might be expected to be less adequate with increasing chamber size, there was no direct relationship between the calculated pulmonary blood volume and the radiologic size of the left atrium (Figure 8). The largest left atrium to brachial artery volumes were recorded among the group of cases with predominant mitral regurgitation, which was associated with the greatest degree of left atrial and left ventricular enlargement. Inordinately high values for pulmonary blood volume were not seen in this group. Experimental evidence indicates that regurgitation into a chamber may greatly facilitate the mixing of injectate therein (6).

The possibility exists that the two indicators may not be thoroughly distributed throughout the entire volume of the left ventricle, but it seems reasonable to expect that the "mixing volume" within that chamber is approximately the same for both indicators. Under these conditions, the mean transit time of the two indicators through the ventricle would be the same.

4. Transit time of indicator and whole blood. It is assumed that the transit time of indicator is the

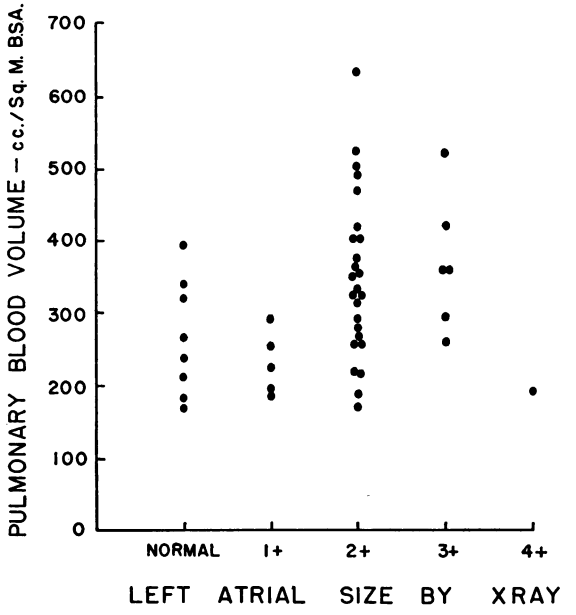

FIG. 8. LEFT ATRIAL CHAMBER SIZE AND PULMONARY BLOOD VOLUME. There is no correlation between the size of the left atrium by X-ray and the calculated pulmonary blood volume.

same as that of whole blood Both the indicators utilized in this study were carried within the plasma fraction. Although there is evidence that the transit time for cells is faster than that for plasma within the central circulation (7), the error introduced into the pulmonary blood volume calculation by this difference is not considered to be significant.

5. Cardiac output. Cardiac output determinations by the indicator dilution method are believed to have an accuracy similar to that of the Fick method, both having an error of about 5 per cent (8, 9). The contribution of technical errors to this percentage should be reduced by obtaining the average of two simultaneous cardiac output determinations with two different indicators. The appearance of recirculating indicator before satisfactory recording of the exponential decay portion of the curve may cause errors in downslope extrapolation which affect both the cardiac output figures and the mean transit time determination in varying degrees. This would be more likely to occur in the dilution curve from pulmonary arterial injection, due to the larger central volume and the longer time required for inscription of the curve. However, the absence of a systematic difference between the pairs of simultaneous cardiac output values, particularly in the range of the very low outputs, suggests that this has not been a source of significant error in these cases (Figure 2). It was necessary to eliminate several cases of severe valvular regurgitation from the study because the prolonged nature of the curves made it difficult to define the exponential decay portion of the curve in the presence of recirculating indicator.

6. Measurement of mean transit time. The timing of the beginning and duration of the two indicator injections was not independently recorded. Injection through the polyethylene catheter into the left atrium requires 0.5 to 1.0 seconds, while injection into the pulmonary artery through the Cournand catheter requires 1.0 to 1.5 seconds. Due to the larger volume of the latter, indicator will not reach the tip of the catheter until a finite length of time after entry of the left atrial indicator into that chamber. The timing of both indicator curves was related to the midpoint of the left atrial injection. This introduces an error in the determination of the mean transit time of the pulmonary arterial indicator, which is assumed not to exceed 0.75 second. The two indicator curves were sampled simultaneously in a fraction collector, thus avoiding a change in the state of the patient. Samples were collected at 2-second intervals, producing a potential error in mean transit time of 1 second. An alternative technique used by McGaff, Jose and Milnor, has been to inject indicators into the pulmonary artery and left atrium consecutively rather than simultaneously and record the time-concentration curve at the brachial artery with a densitometer (10). This has the advantage of potentially improving the accuracy of timing, but the disadvantage of nonsimultaneous determinations. It is currently not possible to record accurately two different dyes simultaneously with two different densitometers.

Because the same aliquots of blood were analyzed for both indicators, errors in the calculated pulmonary mean transit time due to faulty timing of the collecting system, measurement of delay within the sampling catheter, and irregular skewing of the time-concentration curve by the peripheral arterial system have been eliminated.

In considering the above sources of error in the cardiac output and mean transit time determinations, it must be assumed that an over-all error of 20 to 30 per cent may thus be introduced into the calculation of the pulmonary blood volume.

Comparison with previous studies of central blood volume

The circulating blood volume of the pulmonary vascular compartment has defied exact measurement despite Stewart's demonstration in 1897 of the theoretical basis for this calculation (1). Further theoretical and experimental confirmation of the validity of this volume determination, utilizing the product of the mean transit time of indicator particles and the blood flow, has been given repeatedly (2, 11–14).

Investigators have previously calculated "central," "intrathoracic," and "pulmonary" blood volumes by this method. However, the inability to measure the mean transit time of indicator particles traveling from pulmonary artery to left atrium has prevented determination of the pulmonary vascular volume alone. The results of several of the earlier studies are compared with the

TABLE II

Central blood volumes in man *

Compartment	Subjects		Average volume	Average % of total blood volume
	No.	Type		
			ml/m² BSA	
Peripheral vein to systemic artery	91	Normal	1,370	60
Pulmonary artery to systemic artery	76	Normal	650	23
Right ventricle to left ventricle	46	Normal	690	28
	12	Mitral stenosis	609	29
Pulmonary artery to left atrium				
Kunieda (23)	23	Rheum. heart disease	350	12–14†
Milnor and associates (24)	19	Rheum. heart disease	365	12–15†
Present study	45	Rheum. heart disease	322	11–13†

* Stewart-Hamilton method adopted from Lammerant (15).
† Assuming total blood volume = 2.5 to 3.0 L/m² BSA.

volumes found in the present investigation in Table II, with the results grouped according to the vascular compartment measured. This table was adapted from Lammerant (15). The first group of studies (16–20), utilizing peripheral vein injections with sampling from a systemic artery, revealed central volumes averaging 60 per cent of total blood volume comprising the heart, lungs, and large portions of the arterial and venous systems. Pulmonary arterial injections, in the second group, permitted calculation of the blood volume of the lungs, left heart, and part of the systemic arterial compartment, with values averaging 23 per cent of total blood volume (9, 21, 22). Lammerant determined the pulmonary mean transit time from biphasic dilution curves recorded from a precordial surface counter following peripheral vein injection (15). The calculated central volumes, probably including significant portions of the heart chamber volumes, averaged 28 to 29 per cent of the total blood volume.

Kunieda in 1955 (23) and, recently, Milnor, Jose and McGaff (24) have reported values for pulmonary blood volume closely approximating those of the current study, determined by similar methods in comparable groups of patients. The values obtained in these studies are of a significantly lower order of magnitude than those reported by others. Although the total blood volume was not determined, by assuming it to average between 2.5 and 3.0 L per m² BSA (25, 26), the pulmonary blood volume was found to represent approximately 12 per cent of the total blood volume. In the four patients with normal circulatory dynamics, this figure was 9 per cent.

Factors influencing the pulmonary blood volume

A previous report from this laboratory by Rapaport, Kuida, Haynes and Dexter (27) described the general lack of agreement in the literature concerning the extent to which certain factors may influence the volume of the pulmonary vascular compartment. The values obtained in this study, representing what is considered to be a closer approximation to the true pulmonary blood volume, have been correlated with other hemodynamic parameters measured during combined right and left heart catheterization.

Contrary to the findings of Rapaport and coworkers (27), no relationship was noted between cardiac output and pulmonary blood volume. One evident explanation for this divergence of results is that the earlier study contained a smaller number of cases and pertained to the volume of blood between pulmonary artery and brachial artery. The alternate possibility is that the present study included a greater number of patients with severe pulmonary vascular disease, in which case an altered vessel distensibility could obscure a direct flow-volume relationship. No such relationship was evident, however, when the cases exhibiting high pulmonary vascular resistance were segregated from the remainder of the group.

It is reasonable to suspect that pressure eleva-

tion within the left atrium would be reflected by a volume increase in the pulmonary vascular bed and perhaps in the calculated pulmonary blood volume. Indeed, it has been thought that pulmonary "congestion" is responsible for most of the clinical picture associated with mitral valve disease and/or left ventricular failure. A correlation was found in this study between the level of left atrial pressure and pulmonary blood volume, the mean pulmonary blood volume being 277 ml per m^2 in the group of cases with left atrial pressure 15 mm Hg or less, and 357 ml in those patients with atrial pressures above this level (see Figure 7). The difference between these means is statistically significant, the p value being less than 0.02. If those cases with calculated pulmonary vascular resistance above 500 dynes-sec-cm^{-5} are excluded, the effect of elevated left atrial pressure upon pulmonary blood volume is even more evident, the means of these two groups being 264 and 403 ml per m^2 ($p = < 0.01$).

A markedly elevated pulmonary vascular resistance is apparently associated with smaller volumes than would be expected from the pressure-volume relationship seen in the low resistance group. This is not a surprising finding if it is assumed that an elevated pulmonary vascular resistance represents vasoconstriction or mechanical obstruction of the pulmonary vessels. These processes may involve the pulmonary veins as well as arteries. Simon has demonstrated radiologic evidence of regression of engorgement of the pulmonary venous system in a group of cases with severe elevations of left atrial pressures as compared to a group with only moderate left atrial hypertension (28).

Figure 6 shows a similar relationship between the pulmonary arterial pressure and pulmonary blood volume. The association is more evident in the absence of pulmonary vascular disease, when mean pulmonary arterial pressure changes merely reflect rises of left atrial pressures. With the onset of severe elevation of pulmonary vascular resistance, these three parameters no longer exhibit the same dependence upon one another.

As has been pointed out by Burton (29), the factor which determines the volume of a vessel is the transmural pressure, or the difference in pressures within the lumen and exterior of the vessel. This transmural pressure does not necessarily bear a direct relationship to the gradient across a vascular bed from arterial to venous segment. Thus, it is understandable that a correlation was not observed between the pulmonary blood volume and the pressure difference across the pulmonary circulation (pulmonary arterial mean − left atrial mean pressure) or the pulmonary vascular resistance.

In view of the varying severity of the disease process among the diagnostic groups, it was not unexpected that the type of lesion, age, sex, or size of the patient had no apparent influence upon the volume of the pulmonary vascular compartment.

The studies of Lammerant (15) indicate a significant reduction in pulmonary blood volume during exercise and following food intake. Redistribution of blood with the upright position will result in a shift of blood out of the thorax and to the lower extremities. These influences, however, were not in effect in the patients of this study, who were all fasting and in the prone position.

It is apparent that there is no single determining factor governing the pulmonary blood volume in disease states, and it is concluded that a number of opposing influences are in operation whose combined effect is to maintain this volume of blood in the lungs within a relatively narrow range. While it is probable that increased pulmonary venous pressure, by producing distention of that vascular segment and also of the arterial compartment, tends to cause an increase of pulmonary blood volume, at the same time pulmonary vasoconstriction or vascular obliteration may be present and exert an opposite effect. Under such conditions the pulmonary blood volume as a whole might show no dramatic change.

SUMMARY

A method for the measurement of pulmonary blood volume in man has been described, utilizing the product of the cardiac output and the pulmonary mean transit time as determined by simultaneous indicator injections into pulmonary artery and left atrium.

The method has been applied to the study of 45 patients during combined right and left heart catheterization. The assumptions on which this

method is based are discussed, possible sources of error are considered, and the results are compared with previous studies of the pulmonary blood volume. The values obtained are essentially the same as those reported by Kunieda and Milnor and associates. They are significantly smaller than those previously reported by others, and are thought to approach more closely the true volume of the pulmonary vascular compartment.

In the absence of severe pulmonary vascular disease, there appears to be a direct relationship between the volume of blood in the lungs and the pressure within the pulmonary venous system. However, in the presence of vasoconstriction or mechanical obstruction of the pulmonary vessels, as reflected by an elevated vascular resistance, this relationship is altered and further elevations in pressure are not accompanied by volume increases of the same magnitude.

It is evident that a number of interrelated and opposing forces determine the volume of blood in the lungs, and their combined effect is to maintain this volume within a relatively narrow range.

REFERENCES

1. Stewart, G. N. Researches on the circulation time and on the influences which affect it. IV. The output of the heart. J. Physiol. (Lond.) 1897, **22**, 159.
2. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Amer. J. Physiol. 1932, **99**, 534.
3. Björk, V. O., Malmström, G., and Uggla, L. G. Left auricular pressure measurements in man. Ann. Surg. 1953, **138**, 718.
4. Gregersen, M. I. A practical method for the determination of blood volume with the dye T-1824. J. Lab. clin. Med. 1944, **29**, 1266.
5. Parker, B. M., and Smith, J. R. Pulmonary embolism and infarction. A review of the physiologic consequences of pulmonary arterial obstruction. Amer. J. Med. 1958, **24**, 402.
6. Phinney, A. O. Personal communication.
7. Dow, P., Hahn, P. F., and Hamilton, W. F. The simultaneous transport of T-1824 and radioactive red cells through the heart and lungs. Amer. J. Physiol. 1946, **147**, 493.
8. Werkö, L., Lagerlof, H., Bucht, H., Wehle, B., and Holmgren, A. Comparison of the Fick and Hamilton methods for the determination of cardiac output in man. Scand. J. clin. Lab. Invest. 1949, **1**, 109.
9. Doyle, J. T., Wilson, J. S., Lépine, C., and Warren, J. V. An evaluation of the measurement of the cardiac output and of the so-called pulmonary blood volume by the dye-dilution method. J. Lab. clin. Med. 1953, **41**, 29.
10. McGaff, C. J., Jose, A. D., and Milnor, W. R. Pulmonary, left heart and arterial volume in valvular heart disease. Clin. Res. 1959, **7**, 230.
11. Meier, P., and Zierler, K. L. On the theory of the indicator-dilution method for measurement of blood flow and volume. J. appl. Physiol. 1954, **6**, 731.
12. Dow, P. Estimations of cardiac output and central blood volume by dye dilution. Physiol. Rev. 1956, **36**, 77.
13. Braunwald, E., Cournand, A., and Fishman, A. P. Evaluation in a model of Stewart-Hamilton and Bradley methods for measurement of volume of vascular segments. Fed. Proc. 1955, **14**, 17.
14. Schlant, R. C., Novack, P., Kraus, W. L., Moore, C. B., Haynes, F. W., and Dexter, L. The determination of central blood volume. A comparison of the Stewart-Hamilton method with direct measurements in dogs. Amer. J. Physiol. 1959, **196**, 499.
15. Lammerant, J. Le Volume Sanguin des Poumons Chez l'Homme. Bruxelles, Editions Arscia, 1957.
16. Kopelman, H., and Lee, G. de J. The intrathoracic blood volume in mitral stenosis and left ventricular failure. Clin. Sci. 1951, **10**, 383.
17. Ball, J. D., Kopelman, H., and Witham, A. C. Circulatory changes in mitral stenosis at rest and on exercise. Brit. Heart J. 1952, **14**, 363.
18. Etsten, B., and Li, T. H. Hemodynamic changes during thiopental anesthesia in humans: Cardiac output, stroke volume, total peripheral resistance, and intrathoracic blood volume. J. clin. Invest. 1955, **34**, 500.
19. Monge, C. C., Cazorla, A. T., Whittembury, G. M., Sakata, Y. B., and Rizo-Patron, C. A description of the circulatory dynamics in the heart and lungs of people at sea level and at high altitude by means of the dye dilution technique. Acta physiol. latamer. 1955, **5**, 198.
20. Mills, H., and Kattus, A. A., Jr. A comparison of volumes calculated from median circulation time and from slope of human dye dilution curves. J. Lab. clin. Med. 1956, **48**, 413.
21. Doyle, J. T., Wilson, J. S., Estes, E. H., and Warren, J. V. The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. J. clin. Invest. 1951, **30**, 345.
22. Doyle, J. T., Wilson, J. S., and Warren, J. V. The pulmonary vascular responses to short-term hypoxia in human subjects. Circulation 1952, **5**, 263.
23. Kunieda, T. Determination of pulmonary blood volume in patients with mitral valve disease by T-1824 dye method. Kokyu to Junkan 1955, **3**, 510.

24. Milnor, W. R., Jose, A. D., and McGaff, C. J. Pulmonary vascular volume, resistance, and compliance in man. Circulation 1960, **22**, 130.
25. Gibson, J. G., 2nd, and Evans, W. A., Jr. Clinical studies of the blood volume. I. Clinical application of a method employing the azo dye "Evans blue" and the spectrophotometer. J. clin. Invest. 1937, **16**, 301.
26. Gibson, J. G., 2nd, and Evans, W. A., Jr. Clinical studies of the blood volume. II. The relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans. J. clin. Invest. 1937, **16**, 317.
27. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L. The pulmonary blood volume in mitral stenosis. J. clin. Invest. 1956, **35**, 1393.
28. Simon, M. The pulmonary veins in mitral stenosis. J. Fac. Radiol. (Lond.) 1958, **9**, 25.
29. Burton, A. C. The relation between pressure and flow in the pulmonary bed *in* Pulmonary Circulalation, W. Adams and I. Veith, Eds. New York, Grune and Stratton, 1959, p. 26.